COMPARISON OF PROPOFOL WITH THIOPENTONE FOR TREATMENT OF BUPIVACAINE-INDUCED SEIZURES IN RATS

J. E. HEAVNER, J. ARTHUR, J. ZOU, K. McDaniel, B. TYMAN-SZRAM AND P. H. ROSENBERG

SUMMARY

Thirty Sprague–Dawley rats were paralysed with pancuronium and their lungs ventilated mechanically with 70% nitrous oxide and 0.5% halothane in oxygen. Bupivacaine 2 mg kg⁻¹ min⁻¹ was infused continuously i.v. until the animals died. At the onset of seizures, animals were given an i.v. bolus of propofol 1 mg kg⁻¹ (n = 10), thiopentone 2 mg kg⁻¹ (n = 10) or lipid vehicle (n = 10). Administration of propofol or thiopentone was repeated each time seizures restarted and lipid vehicle administrations were repeated at 2-min intervals until the electroencephalogram became isoelectric. All animals developed seizures, arrhythmias, isoelectric EEG and asystole. Administration of lipid vehicle induced no obvious changes in ongoing epileptiform activity. The initial doses of thiopentone and of propofol stopped epileptiform activity in all animals, usually within 6 s after administration. The seizure-free period after the initial administration of thiopentone and of propofol lasted, on average, 0.98 min and 1.72 min, respectively. We conclude that propofol may have value in treating seizures induced by bupivacaine.

KEY WORDS


Thiobarbiturates, particularly thiopentone, are effective in stopping local anesthetic-induced seizures [1]. The increasing use of propofol for sedation and induction and maintenance of anesthesia increases the likelihood that it may be available when a patient suffers a local anesthetic-induced seizure. Propofol has anticonvulsant activity [2–4] but, to our knowledge, its effectiveness in stopping local anesthetic-induced seizures has not been studied.

The objectives of this study were to determine if propofol terminated bupivacaine-induced seizures in lightly anesthetized rats and to compare its efficacy with that of thiopentone.

METHODS

After obtaining approval by the Institutional Animal Care and Use Committee of Texas Tech University Health Sciences Center, we studied 30 Sprague–Dawley rats (222–326 g). Anaesthesia was induced with 2% halothane in oxygen in a 1-litre container. Halothane was administered by mask while the trachea was cannulated via a tracheostomy. The lungs were ventilated using a rodent ventilator (Harvard Apparatus, South Natick, Massachusetts), with a tidal volume of 10 ml kg⁻¹ at a frequency of 50 b.p.m. Needle electrodes were placed for recording leads I, II, and modified VII of the electrocardiogram (ECG) and fronto-occipital electroencephalogram (EEG). Anaesthesia was maintained with 1–1.5% inspired halothane in oxygen while a cannula was placed in each femoral artery for blood sampling and arterial pressure (AP) measurements. A cannula was placed via a femoral vein into the vena cava and advanced to the level of the diaphragm for infusion of bupivacaine and another was placed in the opposite femoral vein for administration of other drugs (see below). ECG, EEG and AP were monitored on a chart recorder (Grass Medical Instruments, Quincy, Massachusetts). Mean AP (MAP) was calculated from the formula MAP = DAP + (SAP − DAP)/3 (DAP = diastolic AP and SAP = systolic AP).

After surgery was completed, pancuronium 1.0 mg kg⁻¹ was given i.v. to induce muscle paralysis and anaesthesia was changed to 0.5% halothane and 70% nitrous oxide in oxygen at least 30 min before the start of i.v. infusion of bupivacaine 2 mg kg⁻¹ min⁻¹. Arterial blood-gas tensions were measured about 10 min before the start of the infusion and ventilation adjusted to achieve Paco₂ approximately 4.6 kPa. Blood-gas measurement was repeated after 5 min if ventilation was adjusted (0.3 ml per sample; never more than two samples). At the onset of seizures, thiopentone 2 mg kg⁻¹, propofol 1 mg kg⁻¹ or propofol vehicle 1 ml kg⁻¹ (Liposyl II 10% Abbott Laboratories, North Chicago, IL) was injected rapidly i.v. A 0.2% thiopentone solution was prepared using saline as diluent, and a 0.1% solution of propofol was

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arrhythmias, isoelectric EEG and asystole. Seizures

MAP, HR and blood-gas values before infusion of
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P vs bupivacaine dose. Statistical significance was
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asystole

was administered each time epileptiform activity
appeared on the EEG. Epileptiform activity was
defined as large amplitude (>$100 \mu V$) repetitive
sharp waves or spikes accompanied by facial
 twitching in animals with incomplete neuromuscular
block. In the Liposyl group, lipid vehicle was
injected at 2-min intervals. Arterial blood samples
(1 ml) for measurement of bupivacaine concentra-
tions were obtained before the start of bupivacaine
infusion and at 2.5-min intervals until the animal
died. Blood was replaced with an equal volume of
isotonic saline. Doses of bupivacaine producing the
following toxic end-points were determined: ar-
rhythmia (cardiac rhythm disturbance accompanied
by an abnormal pulsation on the AP trace); seizures
(appearance of epileptiform activity on the EEG);
isolectric EEG (flattening of the EEG trace);
asytrole (the last recognized beat on the ECG,
allowing 1 min for additional beats to appear).

Doses of bupivacaine concentrations in plasma were
measured by HPLC with ultraviolet detection [5] (lower
limit detection 0.5 $\mu$g ml$^{-1}$; coefficient of variation
(5 $\mu$g ml$^{-1}$) was < 3%).

Statistical analysis

One-way analysis of variance (ANOVA) and the
Student–Newman–Keuls test were used to compare
differences between groups for plasma concentra-
tions and threshold doses of bupivacaine, baseline
values for mean arterial pressure, heart rate and
arterial blood-gas tensions, and differences within
groups for threshold doses of bupivacaine. Chi-
square proportional analysis was used to test for
significant differences between groups with respect
to occurrence of arrhythmias before seizures and
asytrole vs ventricular beats as the terminal ECG
pattern. Multiple analysis of variance (MANOVA)
and Exact $F$ test statistics were used to compare HR
and MAP vs time for the three treatment groups.

Probit analysis was used to analyse cumulative
number of animals with asystole or with sinus arrest
vs bupivacaine dose. Statistical significance was
accepted at $P \leq 0.05$.

RESULTS

MAP, HR and blood-gas values before infusion of
bupivacaine were similar for the treatment groups
(table I).

Toxic endpoints. All animals developed seizures,
arhythmias, isoelectric EEG and asystole. Seizures

occurred first, with the exception of five animals
which experienced arrhythmias before seizure (two
in the Liposyl group, two in the thiopentone group
and one in the propofol group).

The doses of bupivacaine that induced the first
seizure were similar for all three treatment groups
(fig. 1). Because therapeutic intervention began as
soon as seizures started, this toxic endpoint was the
only one that occurred before administration of
Liposyl, thiopentone or propofol (with the exception
of arrhythmias in the five animals that had arrhyth-
mas before seizures). The other toxic endpoints,
therefore, were subject to treatment influences.

Doses of bupivacaine that induced arrhythmias,
isolectric EEG and asystole were greater in the
propofol treatment group compared with the other
treatment groups (data from the five animals that had
arrhythmias before seizures were not included in this
comparison because treatment was instituted after
the arrhythmias). Doses of bupivacaine that induced
arrhythmias and isoelectric EEG were significantly
smaller in the thiopentone group compared with the
propofol group (fig. 1).

While doses of bupivacaine that produced
arrhythmias and isoelectric EEG were not signifi-
cantly different within treatment groups, the
order in which arrhythmias and isoelectric EEG
developed was significantly different in the thio-
pentone group. Arrhythmias occurred first more
often (five of eight animals) in the thiopentone group
than in the lipid vehicle (one of eight) and propofol
groups (three of nine).

Anticonvulsant effect. Liposyl injections induced

<table>
<thead>
<tr>
<th>Weight</th>
<th>pH</th>
<th>$P_{\text{HCO}_3}$</th>
<th>$P_{\text{CO}_2}$</th>
<th>$\text{BE}$</th>
<th>$\text{MAP}$</th>
<th>HR</th>
</tr>
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<td>g</td>
<td></td>
<td>(kPa)</td>
<td>(kPa)</td>
<td>(mmol litre$^{-1}$)</td>
<td>(mmHg)</td>
<td>(beat min$^{-1}$)</td>
</tr>
<tr>
<td>Liposyl</td>
<td>241.5</td>
<td>7.38 (0.05)</td>
<td>4.8 (0.6)</td>
<td>15.4 (2.1)</td>
<td>22.3 (3.1)</td>
<td>-1.28 (3.4)</td>
</tr>
<tr>
<td>Propofol</td>
<td>270.1</td>
<td>7.42 (0.03)</td>
<td>4.4 (0.7)</td>
<td>14.9 (1.8)</td>
<td>21.9 (3.3)</td>
<td>-1.07 (3.1)</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>233.5</td>
<td>7.38 (0.04)</td>
<td>5.1 (1.0)</td>
<td>15.1 (2.0)</td>
<td>22.5 (2.9)</td>
<td>-1.52 (2.3)</td>
</tr>
</tbody>
</table>

Fig. 1. Doses of bupivacaine producing the various toxic endpoints. Data from animals that developed arrhythmias before seizures were excluded from the arrhythmias calculation. * Propofol (●) significantly different (P < 0.05) from thiopentone (□). □ = Lipid vehicle.
no obvious changes in ongoing epileptiform activity. The initial doses of thiopentone and of propofol stopped epileptiform activity in all animals (fig. 2), usually within 6 s. The mean (SD) seizure-free periods after the initial injection of thiopentone and of propofol were 0.98 (0.6) min and 1.72 (1.25) min, respectively (ns). Repeat injections of thiopentone or propofol stopped seizures (except for the third and fourth injections of propofol in one rat which received four injections). The number of times seizures appeared and thiopentone (4.6 (1.7) times) or propofol (6.6 (3.9) times) was administered varied in each group, as did the duration of seizure-free periods. However, the differences between groups were not significant.

Cardiovascular changes. As bupivacaine dose increased, HR decreased, as did MAP after an initial small increase (significant changes over time). The rate of HR change was greater in the thiopentone group compared with the two other groups, but not significantly so. However, MAP decreased significantly faster in the thiopentone group compared with the propofol and lipid vehicle groups (fig. 3). Lipid vehicle injections every 2 min had no effect on arterial pressure. Thiopentone injections usually induced a slight increase in MAP, followed by a transient decrease; propofol induced a transient decrease in MAP. There was no significant difference in MAP decrease induced by the initial injection of propofol or thiopentone (fig. 4).

The terminal ECG pattern preceding asystole was either sinus or ventricular beats. The terminal ECG pattern was ventricular in seven of 10 animals in the thiopentone group, five of 10 animals given propofol and four of 10 given Liposyl (table II). Doses of bupivacaine producing sinus arrest were significantly smaller in the thiopentone group compared with the propofol group. The doses producing this effect in the Liposyl group did not differ significantly from the doses of bupivacaine producing sinus arrest in the two other groups.

Drug concentrations. Plasma concentrations of bupivacaine in the three treatment groups were similar (fig. 5).
FIG. 3. HR vs bupivacaine infusion time (upper graph) and MAP vs bupivacaine infusion time (lower graph). n = 10 until 10 min for lipid vehicle (x) and thiopentone (A), and until 12.5 min for propofol (○), then progressively fewer as animals died.

FIG. 4. Changes in MAP induced by initial doses of thiopentone (△) and propofol (■). A = Just before propofol or thiopentone injection; B = greatest pressure after injection; C = smallest pressure after injection.

TABLE II. Terminal ECG pattern preceding asystole

<table>
<thead>
<tr>
<th></th>
<th>Sinus arrest</th>
<th>Ventricular beats</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposyl</td>
<td>6</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Propofol</td>
<td>5</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>2</td>
<td>7</td>
<td>1</td>
</tr>
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</table>

DISCUSSION

In this study, the anticonvulsant actions of propofol and thiopentone were similar, even though the dose of propofol (1 mg kg⁻¹) was 50% that of thiopentone (2 mg kg⁻¹); the relative potency of propofol and thiopentone for this effect is thus similar to their relative hypnotic potency [6]. Similar effects of these two drugs may be expected because it is thought that propofol, in common with the barbiturates, exerts its anticonvulsant, sedative, hypnotic and anaesthetic effects, at least in part, by enhancing GABA-mediated chloride ion conductance in some neuronal systems [7].

The short duration of anticonvulsant action of thiopentone and propofol is not surprising, given their pharmacokinetic characteristics—rapid redistribution [8], and the fact that bupivacaine infusion was continued at a relatively rapid rate after thiopentone or propofol was injected. In mice, the sleeping time induced by propofol 5 mg kg⁻¹ i.v. is about 3 min [9].

There is some evidence that propofol may be preferable to thiopentone for treatment of bupivacaine-induced seizures; for example, the cumulative percentage asystole vs bupivacaine dose and cumulative percentage sinus arrest vs bupivacaine dose curves for the thiopentone group were to the left of those for the lipid vehicle and propofol groups. Also, the doses of bupivacaine that induced arrhythmias and isoelectric EEG were significantly smaller in the thiopentone group compared with the propofol group.

The effects of propofol and thiopentone on the heart are qualitatively, but not quantitatively, similar. For instance, both depress myocardial contractility, but for an equivalent anaesthetic effect, propofol depresses myocardial contractility less than thiopentone [10, 11].

Propofol increases coronary blood flow markedly; thiopentone does not [12]. It is interesting that intracoronary injection of bupivacaine decreases coronary blood flow [13]. The decrease is accompanied by, and presumably caused by, a decrease in myocardial oxygen consumption. Positive and negative benefits might be produced if propofol antagonizes the effects of bupivacaine on coronary blood flow. A beneficial effect might include increased oxygen and nutrient delivery and increased washout...
of bupivacaine and metabolic wastes (e.g. lactate, and carbon dioxide). A detrimental consequence of increased coronary flow would be increased delivery of bupivacaine to the heart, especially under the conditions of this study, in which bupivacaine was infused continuously.

Light anaesthesia with halothane and nitrous oxide and the use of pancuronium to maintain muscle paralysis may modify toxic responses to bupivacaine. Nevertheless, we conclude that propofol is effective in stopping bupivacaine-induced seizures. Further studies are required to determine if outcomes are better when propofol is used instead of thiopentone. Also, studies comparing propofol and benzodiazepines are required, as one authoritative text indicates that diazepam is the drug of choice for treating local anaesthetic-induced seizures [14].

ACKNOWLEDGEMENTS
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REFERENCES